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(54) Composition for treating renal failure

(57) The invention provides an enteral composition for providing nutrition to renal patients. The enteral composition includes an effective amount of a protein source including whey protein and free amino acids that provide essential as well as nonessential amino acids. The composition is calorically dense and has a moderate osmolality.

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Description

This invention relates to nutritional compositions for the support and therapy of individuals. More specifically, this invention relates to nutritional compositions and methods of using the compositions for preventing or treating renal failure.

Renal failure may be classified as acute or chronic. An abrupt, often reversible impairment (partial or total) of renal function, manifested by inadequate urine formation characterizes acute renal failure (ARF). ARF refers to the clinical conditions associated with rapid, steadily increasing azotemia, with or without oliguria (< 500 mL/day). The causes of ARF can be grouped into three diagnostic categories: pre-renal (inadequate renal perfusion); post-renal (obstruction); and renal. Merck Manual, 16th Edition, p. 1661 (1992).

Patients with ARF very often are subject to such complications as sepsis and hypercatabolism. Using dialysis, the fluid and electrolyte abnormalities of ARF can be regulated, and uremic symptoms reduced. However, dialysis cannot alone prevent the ravages of catabolism, including poor wound healing, the risk of infections and increased mortality. Nutritional support must be used to maintain nutritional status until the ARF improves. Handbook of Clinical Nutrition, 2nd Edition, p. 336 (1989).

In contrast with ARF, chronic renal failure (CRF) refers to the clinical condition resulting from a multitude of pathologic processes that lead to derangement and insufficiency of renal excretory and regulatory function (uremia). CRF may result from any cause of renal dysfunction of sufficient magnitude. The functional effects of CRF can be grouped into three states: diminished renal reserve, renal insufficiency (failure) and uremia. Merck Manual, 16th Edition, p. 1665 (1992).

A gradual destruction of a number of functional nephrons and thus gradual reduction of renal functional capacity characterizes CRF. Progressive CRF produces wasting of both lean and fat body mass, reduced growth rates in children, and diminished synthesis of proteins including albumin. By careful dietary management, especially of protein intake, the progression of CRF may often times be stabilized and dialysis avoided. Handbook of Clinical Nutrition, 2nd Edition, p. 336 (1989).

As an alternate or in conjunction with dialysis, supplying amino acids alone or as dietary supplements has been utilised to support renal failure. While a variety of amino acid mixtures have been utilised, these compositions fail to meet all the necessary nutritional needs of the patient. For example, patients suffering from ARF experience increased energy needs that at times may be increased by as much as 35%. However, at the same time, fluid restriction is critical when treating renal patients.

As a result, patients suffering from renal failure require a high caloric intake with minimal water intake. Inadequate caloric intake contributes to increased protein breakdown and accelerated urea formation. Still further, patients who develop ARF from nephrotoxic drugs or radio-contrast agents require a diet with adequate calories as well as a restricted quantity of high biological value protein. The currently employed formulas fail to adequately meet all these necessary needs of the renal patient with a suitable product formulation.

Therefore, a need exists for a composition for preventing and treating renal failure that supplies sufficient energy with restricted water intake.

Accordingly, in one aspect, this invention provides an enteral composition for treating renal failure, the composition including a therapeutically effective amount of a protein source including free amino acids and whey protein, the protein source have an amino acid profile including L-valine, L-leucine, L-isoleucine, L-threonine, L-methionine, L-lysine, L-phenylalanine, L-tryptophan, L-histidine, L-arginine, L-proline, glycine, L-alanine, L-serine, L-tyrosine, L-cysteine, L-aspartic acid and L-glutamic acid.

The composition is thus an amino acid based, liquid ready-to-use product with a high caloric density and a moderate osmolality. The high caloric density of the product provides patients sufficient energy without high intakes of water. In addition, the moderate osmolality of the product promotes easy tolerance for patients. Therefore the composition is ideally suited for administration to patients at risk of or having renal failure.

The composition preferably provides renal patients with an optimal ratio of essential to non-essential amino acid of about 2:1 to about 4:1. As a result, the high quality protein source enables patients to maintain proper nitrogen balance without excessive protein intake.

Preferably the composition has a caloric density of about 1.6 to about 2.25 kcal/ml.

The composition is preferably supplemented with water soluble vitamins only. This the composition is preferably essentially free of fat soluble vitamins to avoid the possible toxic effects of fat soluble vitamins. Similarly the composition is preferably essentially free of electrolytes. By being virtually electrolyte-free, the composition permits ease of tailoring daily electrolyte needs.

Preferably the composition further comprises a mixture of medium and long-chain triglycerides in a ratio of about 1:1 to about 4:1. The medium-chain triglycerides offer the advantage of being able to satisfy the patient's high caloric requirements without creating fat intolerant conditions.

In another aspect, the invention provides the use of a protein source including whey protein and free amino acids in the preparation of an enteral composition for preventing or treating renal failure in a patient at risk of or having renal

failure, the composition having a caloric density of 1.6 to 2.25 kcal/ml.

In another aspect, the invention provides use of a protein source, including whey protein and free amino acids, and a lipid source in the preparation of an enteral composition for preventing or treating renal failure in a patient at risk of or having renal failure, a lipid source containing medium chain triglycerides and comprising 18% to 28% of the total caloric content of the composition.

The composition is ideally suited for the treatment of acute or chronic renal patients requiring a balanced, low protein diet. Further, because the composition has a very high caloric density, it provides patients sufficient energy with restricted water intake. Moreover, the composition promotes ease of adjusting daily fluid needs.

The composition is convenient to use because it may be provided in a shelf-stable, ready-to-use liquid form. Further, the risk of contamination during preparation is reduce.

Additional features and advantages of the invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments.

Embodiments of the invention are now described by way of example only.

The kidneys play a critical role in maintaining the body's physiologic milieu. The kidneys excrete, secrete, synthesize, regulate, and degrade metabolic substances as well as participate in the metabolism of hormones. When these functions deteriorate as a result of renal failure, various metabolic abnormalities occur that impinge on nutritional status. Moreover, as renal failure progresses, accumulation of toxic substances further affects the body's nutritional and metabolic states, causing an increased requirement for nutrients.

Nutritional support of patients requires prevention, recognition and treatment of nutritional depletion that may occur with illness, such as renal failure. The goals of nutritional support include stabilising metabolic state, maintaining body mass, and/or facilitating growth in the presence of disease. With respect to renal failure, the role of nutritional support is to prevent or reverse associated malnourished states, minimise the adverse effects of nutrients and metabolites that are inadequately excreted, and favourably affect the progression and outcome of renal failure.

This invention provides a product that is specifically directed to meet the needs of patients suffering from renal failure. To this end, the invention provides an amino acid based, liquid ready-to-use composition having a very high caloric density with a moderate osmolality.

Due to a variety of factors, uremic patients suffering from renal failure are often in a negative nitrogen balance and tend to lose muscle mass. In order to counteract such conditions, the composition incorporates a protein source having a specially blended amino acid profile that is specifically designed for renal patients. The protein source contains free amino acids and whey protein.

The composition preferably provides an optimal essential amino acid to non-essential amino acid ratio ranging from approximately 2:1 to 4:1. For example, the essential to non-essential amino acid ratio is approximately 2:1. In such a composition, the essential amino acids may provide 23.0 g/l and the nonessential amino acids may provide 11.4 g/l of the composition. The resulting high quality protein source enhances nitrogen utilisation in the uremic patient by providing the needed precursors for protein synthesis in proportions that minimise excessive formation of urea.

As one skilled in the art will appreciate, the whey protein used in the composition can be in a variety of forms without departing from the scope of the invention. For example, the whey protein can be an intact protein and/or hydrolyzed protein (i.e. peptides produced by a protein degradation).

The specific amino acid profile of the composition provides the key advantages outlined above for the treatment of renal failure patients. The amino acid profile preferably contains the following amino acids in the approximate recited mole percent ranges.

Amino Acid	Mole Percent Ranges
L-Valine	12.3 to 14.8
L-Leucine	8.0 to 9.7
L-Isoleucine	6.8 to 8.2
L-Threonine	5.7 to 6.9
L-Methionine	6.5 to 7.9
L-Lysine	5.5 to 6.6
L-Phenylalanine	5.3 to 6.4
L-Tryptophan	1.4 to 1.6
L-Histidine	6.3 to 7.6
L-Arginine	6.1 to 7.4
L-Proline	3.9 to 4.8
Glycine	7.1 to 8.6
L-Alanine	6.1 to 7.4
L-Serine	3.0 to 3.7
L-Tyrosine	0.5 to 0.8
L-Cysteine	0.6 to 1.1
L-Aspartic Acid	2.0 to 3.4
L-Glutamic Acid	2.7 to 4.7

The protein source of the composition preferably provides approximately 5 to 10% of the total calories of the composition. For example, the protein source comprises approximately 6.9% of the total calories of the composition. This amount coupled with the ratio of essential to non-essential amino acids helps maintain a positive nitrogen balance with low protein intake, while contributing to the control of uremia.

Carbohydrates preferably provide approximately 50% to 65% of the total caloric content of the composition. For example, the carbohydrate source is approximately 58.1 % of the total caloric content of the composition. A number of carbohydrates can be used, including maltodextrin and hydrolyzed corn starch.

The lipid source of the composition includes a mixture of medium-chain triglycerides (MCT) and long-chain triglycerides (LCT). The lipid source provides approximately 25% to about 40% of the caloric content of the composition. For example, the lipid source provides approximately 35% of the caloric content of the composition. This amount coupled with the use of MCTs provides a calorically-dense energy source that allows for better fat absorption.

The lipid profile of the composition is designed to meet essential fatty acid needs (omega-3 and omega-6) while also keeping MCT content high and LCT content low compared with prior formulas. For example, the lipid source includes at least 70% medium-chain triglycerides. In a preferred embodiment, the medium-chain triglyceride source is fractionated coconut oil.

The use of MCTs in the lipid source provides a variety of benefits over prior formulations. For instance, the inclusion of MCT oil ensures that the diet may be used in patients with concomitant malabsorption syndromes, which often occurs in patients with renal failure. Such medium-chain triglycerides are easily absorbed and metabolized in the renal patient. Moreover, the preferred 70:30 ratio sufficiently satisfies patients' high caloric requirements without creating fat intolerant conditions. The composition provides a more calorically dense energy source as compared with products comprised of only long-chain triglycerides.

The remainder of the lipid source is a mixture of long-chain triglycerides. Suitable sources of long-chain triglycerides are canola oil, corn oil, soy lecithin and residual milk fat. The lipid profiles containing such long-chain triglycerides are designed to have a polyunsaturated fatty acid omega-6 (n-6) to omega-3 (n-3) ratio of approximately 1:1 to 10:1. In an embodiment, the composition includes an omega-6 to omega-3 ratio of 4:1.

In addition to the requirements for protein, carbohydrate and lipid, renal patients also have elevated requirements

of certain vitamins, minerals and trace elements. The composition includes a specialised vitamin profile. However, the electrolytes and minerals are excluded or minimised to allow flexibility in the adding of minerals/electrolytes for the prescribing caretaker.

Preferably, the composition provides 100% of the U.S. RDA of vitamins in 2000 kcal. In an embodiment, composition includes only water-soluble vitamins. Water-soluble vitamins, which are lost in dialysis, are often deficient in uremic patients. Fat soluble vitamins, which are not lost during dialysis and can accumulate to toxic levels, are excluded from the composition to avoid their possible toxic effects.

Certain key vitamins are added at increased levels in order to meet the specific needs of the renal patient. For example, hyperphophatemia can inhibit folate uptake in the cell. As a result, the composition preferably includes at least 150% of the U.S. RDA of folic acid. Likewise, pyridoxine metabolism is altered in uremia, and deficiencies are likely to develop. Thus, the composition preferably includes at least 350% of the U.S. RDA of vitamin B_6.

With respect to the supplemented select minerals, only those minerals that are beneficial to the patients' conditions are added. In this regard, zinc as well as selenium are supplemented to prevent possible deficiencies of same. In an embodiment, 10 to 30 mg per 2000 calories of zinc is provided; whereas, 40 to 120 mcg per 2000 calories of selenium is provided. In a preferred embodiment, 14 mg of zinc and 50 mcg of selenium is provided in the composition.

As noted above, the composition is preferably free of electrolytes. Patients with renal failure are unable to excrete electrolytes normally. Thus, through carefully selected ingredients, use of demineralized maltodextrin and electrolyte-free amino acids, the formula is virtually electrolyte free. As a result, the composition minimises accumulation of electrolytes in the blood and permits a clinician controlled intake of these nutrients. Patients have maximum flexibility in customising their diet according to their electrolyte requirements.

The composition is a ready-to-use enteral formulation. Unlike many prior formulations, the composition provides a convenient and easy to use product. Providing the composition in liquid form results in decreased risk of contamination as well as less waste as compared to prior powder formulas.

The composition can be used as a supplement or for total enteral nutritional support. The composition can be tube-fed to a patient, or fed by having the patient drink it. Uniquely, the composition has a moderate osmolality, facilitating easy tolerance for renal patients. In an embodiment, the composition has an osmolality of approximately 400 to 800 mOsm/kg. In a preferred embodiment, osmolality of the composition is approximately 600 mOsm/kg.

Many renal patients have increased energy needs while at the same time are fluid restricted. Therefore, providing high caloric intake to patients is critical for treating renal failure. To this end, the composition not only provides a ready-to-use product but also provides a product that is calorically dense. In an embodiment, the composition has a caloric density of approximately 1.6 kcal/ml to approximately 2.25 kcal/ml. Preferably, the caloric density of the composition is 2.0 kcal/ml. The composition thereby provides patients sufficient energy with restricted water intake.

The composition is preferably utilised to treat or prevent renal failure. Typically, on average, approximately 2000 kcal of the composition will be given per day to a renal patient. Of course, some patients with very high requirements will require substantially more composition and some patients with lower requirements, and/or weights, may require less composition. As one skilled in the art will recognise, the administration of the composition may be varied to refine the responsiveness of the renal failure patient in the particular clinical circumstances at hand. For instance, key factors that affect the amount of composition to be administered include the progress and extent of renal failure, the presence of complications or the disease states, and whether or not dialysis is concurrent. These factors and the degree of dietary protein restriction, if any, are balanced to arrive at optimal maintenance.

The effectiveness of the dietary program may be monitored by well known assays for assessing renal function in dialysed or non-dialysed patients as appropriate. Suitable examples include serum urea nitrogen (SUN), SUN/creatinine ratio, urea nitrogen appearance and glomerular filtration rate for creatinine. Other diagnostic mechanisms will be apparent to the ordinary person skilled in the art.

By way of example, and not limitation, an example of a suitable composition that may be used is as follows.

The composition includes the following ingredients: water; maltodextrin, medium-chain triglycerides, (MCT source: fractionated coconut oil); canola oil; whey protein concentrate; modified corn starch, L-valine; corn oil; L-arginine, L-histidine, L-methionine, L-phenylalanine; L-leucine; L-lysine acetate; L-isoleucine; soy lecithin, glycine; L-threonine L-alanine; L-proline; choline bitartrate; L-tryptophan; L-serine; ascorbic acid; L-carnitine; taurine; zinc sulphate; niacinamide; calcium pantothenate; pyridoxine hydrochloride; biotin; riboflavin; thiamine mononitrate; folic acid; sodium selenate and cyanocobalamin.

The composition has the following nutrient composition (per 500 kcal):

Nutrient Composition	Amount	% U.S. RDA*
Protein	8.6 g	19
Carbohydrate	72.6 g	**
Fat***	20.6 g	**
Water	176 ml	**
Vitamin C	15 mg	25
Vitamin B_1	.38 mg	25
Vitamin B_2	.43 mg	25
Niacin	5 mg	25
Vitamin B_6	1.75 mg	88
Folic Acid	150 mcg	38
Pantoth. Acid	2.5 mg	25
Vitamin B_{12}	1.5 mcg	25
Biotin	75 mcg	25
Choline	100 mg	**
Taurine	25 mg	**
L-Carnitine	25 mg	**
Zinc	3.5 mg	23
Selenium	12.5 mcg	**

* U.S. Recommended Daily Allowance for Adults and Children 4 or More Years of Age
** U.S. RDA Not Established
*** MCT Provides 14.4 grams Per 500 Kcal

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

Claims

1. An enteral composition for treating renal failure comprising:

   a therapeutically effective amount of a protein source including free amino acids and whey protein, the protein source having an amino acid profile comprising L-valine, L-leucine, L-isoleucine, L-threonine, L-methionine, L-lysine, L-phenylalanine, L-tryptophan, L-histidine, L-arginine, L-proline, glycine, L-alanine, L-serine, L-tyrosine, L-cysteine, L-aspartic acid and L-glutamic acid.

2. The use of a protein source including whey protein and free amino acids in the preparation of an enteral composition for preventing or treating renal failure in a patient at risk of or having renal failure, the composition having a caloric density of 1.6 to 2.25 kcal/ml.

3. The composition or use of claim 1 or claim 2 further comprising a mixture of medium and long-chain triglycerides having a ratio of approximately 1:1 to 4:1.

4. The use of a protein source, including whey protein and free amino acids, and a lipid source in the preparation of an enteral composition for preventing or treating renal failure in a patient at risk of or having renal failure, a lipid source containing medium chain triglycerides and comprising 18% to 28% of the total caloric content of the composition.

5. The use of claim 4 in which the lipid source comprises long-chain triglycerides, the medium to long-chain triglycerides ratio being approximately 1:1 to 4:1.

6. The use of claims 2 to 5 in which the protein source has an amino acid profile including L-valine, L-leucine, L-isoleucine, L-threonine, L-methionine, L-lysine, L-phenylalanine, L-tryptophan, L-histidine, L-arginine, L-proline, glycine, L-alanine, L-serine, L-tyrosine, L-cysteine, L-aspartic acid and L-glutamic acid.

7. The composition or use of claims 1, 4 or 5 having a caloric density of 1.6 kcal/ml to 2.25 kcal/ml.

8. The composition or use of claims 1 to 7 in which the protein source has an essential amino acid to nonessential amino acid ratio of approximately 2:1 to 4:1.

9. The composition or use of claims 1 to 8 further comprising water soluble vitamins but being essentially free of electrolytes and fat soluble vitamins.

10. The composition or use of claims 1 to 9 in which the whey protein comprises up to 50% of the protein source.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 20 1536

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 442 140 (MILCHWERKE WESTFALEN EG) 21 August 1991 * claims; page 5 *	1-10	C07K14/47 A61K35/20 //A23C21/00
X	GB-A-1 306 402 (AMERICAN HOME PRODUCTS CO.) 14 February 1973 * claims 14-18; page 1, column 1; tables III-VI *	1-10	
X	AKT. ERNÄHR.-MED., vol. 18, 1993, pages 38-40, XP000578916 MANZ, F. ET AL.: "Special cow's milk formula and special whey protein concentrate ..." * summary; table 1 *	1-10	
A	WO-A-85 03863 (BAXTER TRAVENOL LABORATORIES, INC.) 12 September 1985 * background; summary *	3,5	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07K
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	26 August 1996	Hermann, R

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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